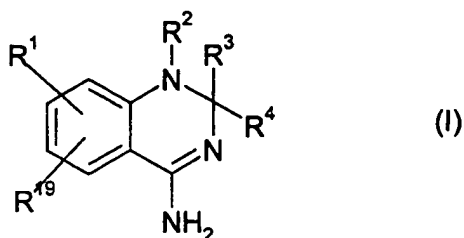


Compounds that selectively inhibit iNOS have been described in US patents 5,132,453 and 5,273,875.

Combination therapies of NSAIDs with other drugs targeted at different mechanisms are known in the art. A combination of the analgesic diflunisal and an antispasmodic compound has been described (Basmajian J., *Spine*, 1989, 14, 438). Also, a combination of ibuprofen with an antispasmodic to reduce morning stiffness in primary fibromyalgia syndrome (Fossaluzza V. and DeVita S., *Int. J. Clin. Pharm. Res.*, 1992, 12, 99) and a combination of tetracycline with flurbiprofen for the treatment of rheumatoid arthritis (Greenwald R. et al, *J. Rheumatol.*, 1992, 19, 927) are known.

However, COX-2 inhibitors (and other NSAIDs) do not have complete efficacy and do not completely overcome the inflammatory condition being treated, even at optimal doses. There is therefore a need to improve the efficacy of COX-2 inhibitors. It has now been found that the efficacy of a COX-2 inhibitor can be improved if it is combined with a iNOS inhibitor, and as a result inflammatory diseases may be treated with a combination of an iNOS inhibitor and a COX-2 inhibitor. Although it has been said that some of the inflammatory actions of iNOS are dependent on the secondary activation of COX and an increase in prostaglandin formation (Salvemini D. et al, *Proc. Nat. Acad. Sci. USA*, 1993, 90, 7240; Salvemini et al, *J. Clin. Invest.*, 1995, 96, 301) it is believed that a combination of selective inhibitors of iNOS and COX-2 will lead to a substantially greater anti-inflammatory efficacy compared with the efficacy of each agent alone. By inhibiting iNOS and COX-2 at inflammatory sites the combination will result in a greater and more complete reduction in the severity of inflammation in a variety of inflammatory diseases and inflammation related disorders.

In a first aspect the invention provides a pharmaceutical combination comprising a COX-2 inhibitor and a compound of formula (I):



wherein:-

R^1 and R^{19} independently represent hydrogen, alkyl C1 to 6, alkoxy C1 to 6, alkylthio C1 to 6, halogen, hydroxyl or amino;

(i) R^3 represents phenyl, a 6-membered heterocyclic aromatic ring containing one or two nitrogen atoms, or a 5-membered heterocyclic aromatic ring containing 1 to 3 heteroatoms selected from O, N and S, which phenyl or heterocyclic aromatic ring may be optionally substituted by alkyl C1 to 6, alkoxy C1 to 6, halogen, hydroxyl, alkylthio C1 to 6, cyano, trifluoromethyl, nitro, hydroxymethyl, amino, a group $-(CH_2)_c \cdot NHCO_2R^{10}$, a group $-(CH_2)_c \cdot NR^5R^6$, or a group $-CO_2R^{11}$, and R^4 represents hydrogen or alkyl C1 to 6; or

(ii) R^3 represents hydrogen or alkyl C1 to 8, which alkyl group may be optionally substituted by amino or a group $-NHCO_2R^{10}$, and R^4 represents hydrogen or alkyl C1 to 6; or

(iii) R^3 and R^4 taken together represent a group $(CH_2)_a \cdot Z \cdot (CH_2)_b$;

c represents zero, 1 or 2;

a and b independently represent an integer 1 to 3;

Z represents CH_2 , NH , a group $>N(CH_2)_n YR^{13}$, a group $>NCOX(CH_2)_n YR^{13}$, a group $>NCSX(CH_2)_n YR^{13}$, or a group $>NCNHX(CH_2)_n YR^{13}$;

X represents O, S or a bond;

Y represents O, S, SO , SO_2 , NR^9 or a bond;

n represents zero or an integer from 1 to 6;

- (a) R^{13} represents alkyl C1 to 6, cyano, quinolyl, phenyl, naphthyl, a 6-membered heterocyclic aromatic ring containing one or two nitrogen atoms, a 5-membered heterocyclic aromatic ring containing 1 to 3 heteroatoms selected from O, N and S, a benzene ring fused with a 5-membered heterocyclic aromatic ring containing 1 to 3 heteroatoms selected from O, N and S or alkyl C1 to 6 substituted by one or more halogen atoms; or
- (b) R^{13} may be as defined in (a) except that when it contains one or more aromatic rings, said rings may be optionally substituted by one or more groups selected from alkyl C1 to 6, halogen, cyano, nitro, hydroxyl, alkoxy C1 to 6, trifluoromethyl, trifluoromethoxy, methanesulphonyl, sulphamoyl, $-NR^{14}R^{15}$, $-COOR^{16}$ or $-CONR^7R^8$; or
- (c) R^{13} may represent a phenyl ring, a 6-membered heterocyclic aromatic ring containing one or two nitrogen atoms, or a 5-membered heterocyclic aromatic ring containing 1 to 3 heteroatoms selected from O, N and S substituted by:
- benzyloxy or optionally substituted phenyl or an optionally substituted 5-membered heterocyclic aromatic ring containing 1 to 3 heteroatoms selected from O, N and S;
- wherein the optional substituents are alkyl C1 to 6, halogen, cyano, nitro, hydroxyl, alkoxy C1 to 6, trifluoromethyl and trifluoromethoxy; or
- (d) R^{13} may be as defined in (a), (b) or (c) except that when it contains a heterocyclic aromatic ring containing at least one nitrogen atom, said ring may be optionally substituted by one or more oxo groups adjacent to the nitrogen, the ring being attached to the remainder of the molecule through one of the nitrogen atoms or otherwise;
- R^2 , R^5 , R^6 , R^{11} , R^9 , R^{14} , R^{15} and R^{16} independently represent hydrogen or alkyl C1 to 6;
- in addition, when Y represents NR^9 , $-NR^9R^{13}$ may together represent a pyrrolidine or piperidine ring;
- R^{10} represents alkyl C1 to 6; and
- R^7 and R^8 independently represent hydrogen, alkyl C1 to 6 or phenyl optionally substituted by one or more groups selected from alkyl C1 to 6, halogen, cyano, nitro, hydroxyl, alkoxy C1 to 6, trifluoromethyl and trifluoromethoxy;

or a pharmaceutically acceptable salt, enantiomer or tautomer thereof.

Such a combination has been found to have pharmaceutical activity, especially for treating inflammatory disease.

5

Another aspect of the invention provides the use of the combination described above, in the manufacture of a medicament, for the treatment or prophylaxis of inflammatory disease.

The invention also provides a method of treatment or prophylaxis of an inflammatory
10 disease in a person suffering from or susceptible to such a disease, which method comprises administering to the person a therapeutically effective amount of the combination.

Preferred iNOS inhibitors for use in the combinations of the invention include compounds
15 known from WO 97/14686. In particular, the compound of formula (I) for use in the present invention can be any of the iNOS inhibitors of Examples 1 to 257 disclosed in WO 97/14686, or any other pharmaceutically acceptable salt, enantiomer or tautomer thereof.

Preferably R^3 and R^4 taken together represent a group $(CH_2)_a \cdot Z \cdot (CH_2)_b$, in which Z
20 represents a group $>NCO(CH_2)_n R^{13}$, a group $>NCS(CH_2)_n R^{13}$, or a group $>NCNH(CH_2)_n R^{13}$ and R^{13} represents optionally substituted phenyl, furyl, thienyl, thiazolyl, isoxazolyl, isothiazolyl, thiadiazolyl, pyridyl or pyrazinyl. In such a case, it is further preferred that n represents zero, and R^{13} represents substituted phenyl or substituted pyridyl, wherein the substituent is in the *para* position.

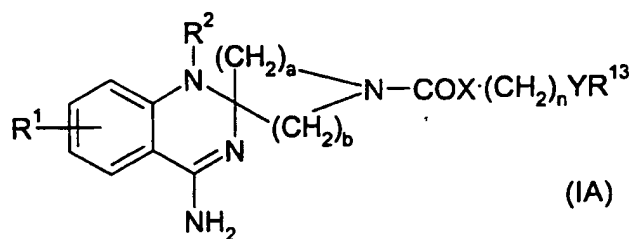
25 Preferably R^1 and R^{19} independently represent hydrogen or halogen, more preferably at least one of R^1 and R^{19} represents fluoro or chloro. R^1 may especially represent 5-fluoro or 5-chloro, and in particular R^1 may represent 5-fluoro and R^{19} 8-fluoro.

When R^3 and R^4 taken together represent a group $(CH_2)_a \cdot Z \cdot (CH_2)_b$, it is preferred that a and b each represent 2.

Preferably R^2 represents hydrogen.

When R^4 represents hydrogen, it is preferred that R^3 represents ethyl, isopropyl, cyclopropyl or cyclobutyl; or furyl, thienyl or substituted phenyl wherein the substituent is fluoro or hydroxyl.

- 5 Alternatively, when R^3 and R^4 taken together represent a group $(CH_2)_a \cdot Z \cdot (CH_2)_b$ in which Z represents a group $>NCO_2(CH_2)_n YR^{13}$ or $>NCSO(CH_2)_n YR^{13}$, it is preferred that n represents 0, Y represents a bond and R^{13} represents alkyl C1 to 6 or chloroalkyl C3 to 6; or n may represent 2, Y represent oxygen and R^{13} represent optionally substituted phenyl or pyridyl.
- 10 In one particular aspect of the invention, the preferred iNOS inhibitor is a compound of formula (IA)



wherein

R^1 represents hydrogen, alkyl C1 to 6, alkoxy C1 to 6 or halogen;

a and b independently represent an integer 1 to 3;

- 15 X represents O, S or a bond;

Y represents O, S, NR^9 or a bond;

n represents an integer 0 to 4;

R^{13} represents alkyl C1 to 6, cyano, trifluoromethyl, phthalimido, quinolyl, phenyl, a 6-membered heterocyclic aromatic ring containing one or two nitrogen atoms, a 5-membered heterocyclic aromatic ring containing 1 to 3 heteroatoms selected from O, N and S or a benzene ring fused with a 5-membered heterocyclic aromatic ring containing 1 to 3 heteroatoms selected from O, N and S;

or R^{13} may be as defined above except that when it contains one or more aromatic rings, said rings may be optionally substituted by one or more groups selected from alkyl C1 to 6,

halogen, cyano, nitro, hydroxy, alkoxy C1 to 6, trifluoromethyl, trifluoromethoxy, sulphonylmethyl, sulphonylamino, $\text{—NR}^{14}\text{R}^{15}$, —COOR^{16} or $\text{—CONR}^7\text{R}^8$;

or R^{13} may represent a phenyl ring substituted by benzyloxy or optionally substituted phenyl or an optionally substituted 5-membered heterocyclic aromatic ring containing 1 to

5 3 heteroatoms selected from O, N and S, wherein the optional substituents are alkyl C1 to 6, halogen, cyano, nitro, hydroxy, alkoxy C1 to 6, trifluoromethyl and trifluoromethoxy;

R^2 , R^{14} , R^{15} , R^{16} and R^9 independently represent hydrogen or alkyl C1 to 6;

in addition, when Y represents NR^9 , $\text{—NR}^9\text{R}^{13}$ may together represent a pyrrolidine or piperidine ring; and

10 R^7 and R^8 independently represent hydrogen, alkyl C1 to 6 or phenyl optionally substituted by one or more groups selected from alkyl C1 to 6, halogen, cyano, nitro, hydroxy, alkoxy C1 to 6 and trifluoromethyl;

provided that:

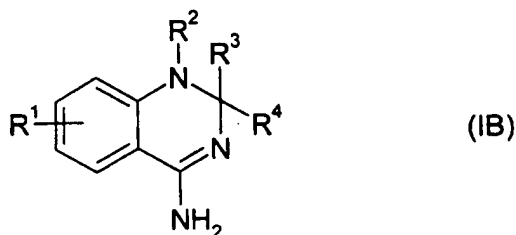
(a) when neither X nor Y represents a bond then n represents an integer 2 to 4;

15 (b) when R^{13} represents cyano then Y represents a bond and either X also represents a bond or X does not represent a bond and n represents an integer 1 to 4;

or a pharmaceutically acceptable salt thereof.

In a further aspect of the invention, the preferred iNOS inhibitor is a compound of formula

20 (IB)



wherein

R^1 represents hydrogen, alkyl C1 to 6, alkoxy C1 to 6, alkylthio C1 to 6 or halogen;

R^3 represents phenyl or a six membered heterocyclic aromatic ring containing 1 to 3 nitrogen

25 atoms, which phenyl or heterocyclic aromatic ring may be optionally substituted by alkyl C1

to 6, alkoxy C1 to 6, halogen, hydroxy, alkylthio C1 to 6, cyano, trifluoromethyl, nitro, hydroxymethyl or a group $\text{—NR}^5\text{R}^6$,

or R^3 represents a five membered heterocyclic aromatic ring containing 1 to 3 heteroatoms selected from O, N or S optionally substituted by alkyl C1 to 6 or halogen,

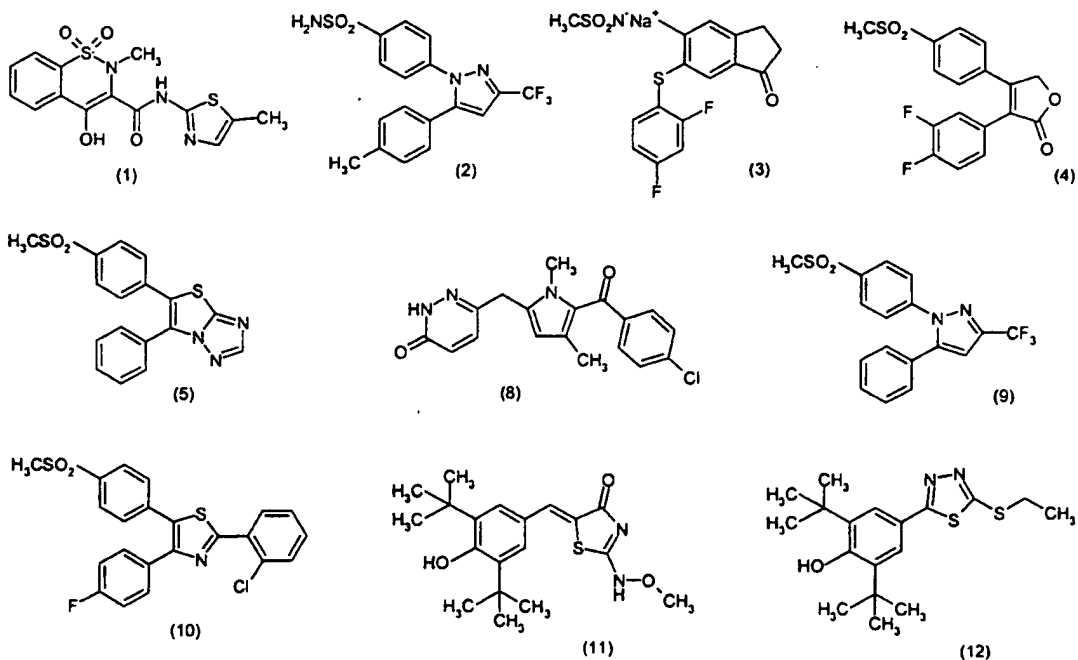
5 or R^3 represents hydrogen or alkyl C1 to 8; and

R^2 , R^4 , R^5 and R^6 independently represent hydrogen or alkyl C1 to 6;

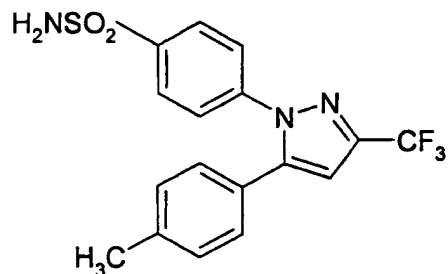
or a pharmaceutically acceptable salt thereof.

Preferred COX-2 inhibitors for use in the combinations of the invention include those

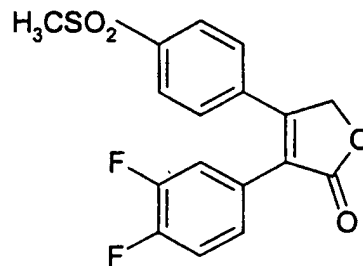
10 disclosed in WO 96/41626, in particular the compound known as Celecoxib (Searle - compound 2 below). Other preferred COX-2 inhibitors for use in the combinations of the invention include those disclosed in Drugs of the Future, 1997, 22, 711 - 714 which document is incorporated herein by reference, namely (1) Meloxicam, (3) L-745337 (Merck), (4) MK-966 (Merck), (5) L-768277 (Merck), GR-253035 (Glaxo-Wellcome), JTE-522
15 (Japan Tobacco), (8) RS-57067-000 (Roche), (9) SC-58125 (Searle), (10) SC-078 (Searle), (11) PD-138387 (Warner-Lambert), NS-398 (Taisho), flosulide and (12) PD-164387 (Warner-Lambert).



More preferably the COX-2 inhibitor is Celecoxib or MK-966:



Celecoxib



MK-966

The combination of an iNOS inhibitor and a COX-2 inhibitor would be used to treat other inflammation associated disorders, such as an analgesic for pain and headaches or as an antipyretic for the treatment of fever. The combination would be used to treat arthritis and other skeletal muscular conditions, for example rheumatoid arthritis, osteoarthritis, spondyloerthritis, gouty arthritis, juvenile arthritis and systemic lupus erythematosus and tendinitis. The combinations would also be used to treat asthma, chronic obstructive pulmonary disease, bronchitis, adult respiratory distress syndrome and other conditions of pulmonary inflammation such as cystic fibrosis and those associated with viral infection. The combination would also be used to treat inflammatory conditions of the skin such as psoriasis, eczema, dermatitis and burns. The combination would also be used to treat inflammatory diseases of the gastrointestinal tract such as inflammatory bowel disease (Crohn's disease and ulcerative colitis), gastritis and peptic ulceration and also irritable bowel syndrome. In addition the combination would also be useful in the treatment of cancer, including colorectal cancer and breast cancer. The combination would also be useful in the treatment of inflammatory conditions of the vascular system such as atherosclerosis, periarteritis nodosa and migraine.

The invention therefore provides a combination as described herein for use in therapy, that is for both treatment and prophylaxis of a disease.

Prophylaxis is expected to be particularly relevant to the treatment of persons who have
5 suffered a previous episode of, or are otherwise considered to be at increased risk of, the
disease or condition in question. Persons at risk of developing a particular disease or
condition generally include those having a family history of the disease or condition, or
those who have been identified by genetic testing or screening to be particularly
susceptible to developing the disease or condition.

10

By the term "combination" is meant any pharmaceutical composition in which the iNOS
inhibitor and the COX-2 inhibitor are administered in a single dosage unit, for example a
single tablet or capsule containing a fixed ratio of the two active ingredients, as well as
combination therapy in which the iNOS inhibitor and the COX-2 inhibitor are administered
15 in separate dosages, that is to say, administration of each agent simultaneously or
sequentially.

In a further aspect the invention relates to a kit comprising one or more unit doses of an iNOS
inhibitor or a pharmaceutically acceptable salt thereof and one or more unit doses of a COX-2
20 inhibitor or a pharmaceutically acceptable salt thereof. Such kits can, for example, be in the
form of blister packs containing each medicament in separate unit doses.

For the above mentioned therapeutic indications, the dosage administered will, of course,
vary with the compound employed, the mode of administration and the treatment desired.
25 However, in general, satisfactory results are obtained when the compounds are administered
at a daily dosage of the solid form of between 1 mg and 2000 mg per day.

The combinations of the invention may be used on their own, or preferably as a
pharmaceutical composition in which the compounds or derivatives are in admixture with a
30 pharmaceutically acceptable adjuvant, diluent or carrier. For example in a form appropriate

for enteral or parenteral administration. The pharmaceutical composition preferably comprises less than 80% and more preferably less than 50% of the compound or derivative. Examples of suitable adjuvants, diluents and carriers are well known to a person skilled in the art and include microcrystalline cellulose, calcium phosphate, diatomaceous earth, a sugar
5 such as lactose, dextrose or mannitol, talc, stearic acid, starch, sodium bicarbonate and/or gelatin.

According to a further aspect of the invention there is provided a pharmaceutical composition comprising a combination of an iNOS inhibitor and a COX-2 inhibitor as
10 hereinbefore defined in association with a pharmaceutically acceptable adjuvant, diluent or carrier.

According to a further aspect of the invention there is thus provided the use of a combination of an iNOS inhibitor and a COX-2 inhibitor as hereinbefore defined or a
15 pharmaceutically acceptable salt or solvate thereof, in the manufacture of a medicament for the treatment or prophylaxis of a reversible obstructive airways disease.

In a further aspect the invention provides a method of treatment or prophylaxis of inflammatory conditions which comprises administering to a host suffering from or
20 susceptible to such conditions a combination of an iNOS inhibitor and a COX-2 inhibitor as hereinbefore defined in association with a pharmaceutically acceptable adjuvant, diluent or carrier.

The invention is illustrated by the experimental data given below.

25

**Assessment of anti-inflammatory activity in the rat carrageenan paw oedema
(C. A. Winter et al., Proc. Soc. Exp. Biol. Med. 1962, 111, 544)**

Inflammation was induced in the right hind paw of 180-250g Charles River CD male rats
30 by the injection of 0.1ml of 1% carrageenan (Marine Colloids) in saline into the plantar region of the foot. Paw volume was measured by plethysmography before carrageenan

injection and at 2, 4 and 6 hours after the intra-plantar injection. Paw oedema for each rat was calculated as the increase in paw volume over the initial paw volume measured prior to carrageenan injection. Inhibition of oedema for the treatments was calculated as a percentage inhibition of the mean absolute increase in foot volume in treated animals compared to control animals.

The rats were housed on sawdust and fasted overnight prior to the day of the experiment (water available *ad libitum*). The animals had free access to 5% glucose in water throughout the course of the experiment, and were re-fed after the 4 hour measurement.

The ankle joint of each right hind paw was marked the day prior to the experiment to indicate the level to which the paw volume would be measured in the experiment.

Carrageenan was prepared the day prior to the experiment by suspending carrageenan in saline (1% w/v) and stirring vigorously on a magnetic stirrer for at least one hour. The suspension was stored at 4°C until required and allowed to reach room temperature prior to use. The drugs were administered to groups of 6 rats 30 mins prior to carrageenan injection either orally (5ml/kg) or subcutaneously (2ml/kg). The COX-2 inhibitors were prepared for oral dosing in suspensions in 0.25% carboxymethylcellulose containing 1.5% Tween 80 (sonicated until dispersed). The iNOS inhibitor was dosed subcutaneously in 6% glucose in distilled water (dissolved by sonication for 5 min).

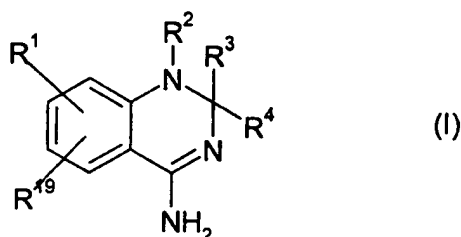
An iNOS inhibitor or COX-2 inhibitor alone only produced a partial block of the inflammatory response, while a combination of the two produced a higher level of inhibition as shown in the Table below which shows anti-inflammatory activity 4 or 6 hours after administration of the carrageenan:

	Experiment 1 % inhibition	Experiment 2 % inhibition
1. iNOS (n = 6)	35	11
2. COX-2 (n = 6)	35	32
1 and 2 (n = 6)	74	63

1. iNOS = 1-(6-cyano-3-pyridylcarbonyl)-5',8'-difluorospiro[piperidine-4,2'(1'H)-quinazoline]-4'-amine hydrochloride (30 μ mol/kg).
1. COX-2 = Celecoxib (3mg/kg).

CLAIMS

1. A pharmaceutical combination comprising a COX-2 inhibitor or a pharmaceutically acceptable salt thereof and a compound of formula (I):



wherein:-

R¹ and R¹⁹ independently represent hydrogen, alkyl C1 to 6, alkoxy C1 to 6, alkylthio C1 to 6, halogen, hydroxyl or amino;

(i) R³ represents phenyl, a 6-membered heterocyclic aromatic ring containing one or two nitrogen atoms, or a 5-membered heterocyclic aromatic ring containing 1 to 3 heteroatoms selected from O, N and S, which phenyl or heterocyclic aromatic ring may be optionally substituted by alkyl C1 to 6, alkoxy C1 to 6, halogen, hydroxyl, alkylthio C1 to 6, cyano, trifluoromethyl, nitro, hydroxymethyl, amino, a group $-(CH_2)_c \cdot NHCO_2R^{10}$, a group $-(CH_2)_c \cdot NR^5R^6$, or a group $-CO_2R^{11}$; and R⁴ represents hydrogen or alkyl C1 to 6; or

(ii) R³ represents hydrogen or alkyl C1 to 8, which alkyl group may be optionally substituted by amino or a group $-NHCO_2R^{10}$; and R⁴ represents hydrogen or alkyl C1 to 6; or

(iii) R³ and R⁴ taken together represent a group $(CH_2)_a \cdot Z \cdot (CH_2)_b$;

c represents zero, 1 or 2;

a and b independently represent an integer 1 to 3;

Z represents CH_2 , NH, a group $>N(CH_2)_n YR^{13}$, a group $>NCOX(CH_2)_n YR^{13}$, a group $>NCSX(CH_2)_n YR^{13}$, or a group $>NCNHX(CH_2)_n YR^{13}$;

X represents O, S or a bond;

Y represents O, S, SO, SO₂, NR⁹ or a bond;

n represents zero or an integer from 1 to 6;

- (a) R¹³ represents alkyl C1 to 6, cyano, quinolyl, phenyl, naphthyl, a 6-membered
5 heterocyclic aromatic ring containing one or two nitrogen atoms, a 5-membered
heterocyclic aromatic ring containing 1 to 3 heteroatoms selected from O, N and S, a
benzene ring fused with a 5-membered heterocyclic aromatic ring containing 1 to 3
heteroatoms selected from O, N and S or alkyl C1 to 6 substituted by one or more halogen
atoms or
- 10 (b) R¹³ may be as defined in (a) except that when it contains one or more aromatic rings,
said rings may be optionally substituted by one or more groups selected from alkyl C1 to 6,
halogen, cyano, nitro, hydroxyl, alkoxy C1 to 6, trifluoromethyl, trifluoromethoxy,
methanesulphonyl, sulphamoyl, —NR¹⁴R¹⁵, —COOR¹⁶ or —CONR⁷R⁸; or
- (c) R¹³ may represent a phenyl ring, a 6-membered heterocyclic aromatic ring containing
15 one or two nitrogen atoms, or a 5-membered heterocyclic aromatic ring containing 1 to 3
heteroatoms selected from O, N and S substituted by:
benzyloxy or optionally substituted phenyl or an optionally substituted 5-membered
heterocyclic aromatic ring containing 1 to 3 heteroatoms selected from O, N and S;
wherein the optional substituents are alkyl C1 to 6, halogen, cyano, nitro, hydroxyl, alkoxy
20 C1 to 6, trifluoromethyl and trifluoromethoxy; or
- (d) R¹³ may be as defined in (a), (b) or (c) except that when it contains a heterocyclic
aromatic ring containing at least one nitrogen atom, said ring may be optionally substituted
by one or more oxo groups adjacent to the nitrogen, the ring being attached to the
remainder of the molecule through one of the nitrogen atoms or otherwise;
- 25 R², R⁵, R⁶, R¹¹, R⁹, R¹⁴, R¹⁵ and R¹⁶ independently represent hydrogen or alkyl C1 to 6;
in addition, when Y represents NR⁹, —NR⁹R¹³ may together represent a pyrrolidine or
piperidine ring;

R¹⁰ represents alkyl C1 to 6; and

R⁷ and R⁸ independently represent hydrogen, alkyl C1 to 6 or phenyl optionally substituted by one or more groups selected from alkyl C1 to 6, halogen, cyano, nitro, hydroxyl, alkoxy C1 to 6, trifluoromethyl and trifluoromethoxy;

5 or a pharmaceutically acceptable salt, enantiomer or tautomer thereof.

2. A combination as claimed in Claim 1, wherein in formula (I) R³ and R⁴ taken together represent a group (CH₂)_a·Z·(CH₂)_b, in which Z represents a group >NCO(CH₂)_nR¹³, a group >NCS(CH₂)_nR¹³, or a group >NCNH(CH₂)_nR¹³ and R¹³ represents optionally substituted
10 phenyl, furyl, thienyl, thiazolyl, isoxazolyl, isothiazolyl, thiadiazolyl, pyridyl or pyrazinyl.

3. A combination as claimed in claim 2, wherein in formula (I) R¹³ represents substituted phenyl or substituted pyridyl, wherein the substituent is in the *para* position.

15 4. A combination as claimed in claim 2 or claim 3, wherein in formula (I) n represents 0.

5. A combination as claimed in any preceding claim, wherein R³ and R⁴ taken together represent a group (CH₂)_a·Z·(CH₂)_b, in which a and b each represents 2.

20 6. A combination as claimed in claim 1, wherein in formula (I) R⁴ represents hydrogen and R³ represents ethyl, isopropyl, cyclopropyl, cyclobutyl, furyl, thienyl or substituted phenyl wherein the substituent is fluoro or hydroxyl.

7. A combination as claimed in claim 1, wherein in formula (I) R³ and R⁴ taken together
25 represent a group (CH₂)_a·Z·(CH₂)_b, in which Z represents a group >NCO₂(CH₂)_nYR¹³ or >NCSO(CH₂)_nYR¹³.

8. A combination as claimed in claim 7, in which n represents 0, Y represents a bond and R¹³ represents alkyl C1 to 6 or chloroalkyl C3 to 6.
9. A combination as claimed in claim 7, in which n represents 2, Y represents oxygen
5 and R¹³ represents optionally substituted phenyl.
10. A combination as claimed in any preceding claim, wherein in formula (I) R¹ and R¹⁹ independently represent hydrogen or halogen.
- 10 11. A combination as claimed in claim 10, wherein at least one of R¹ and R¹⁹ represents fluoro or chloro.
12. A combination as claimed in claim 11, wherein R¹ represents 5-fluoro or 5-chloro.
- 15 13. A combination as claimed in claim 12, wherein R¹ represents 5-fluoro and R¹⁹ represents 8-fluoro.
14. A combination as claimed in any preceding claim, wherein in formula (I) R² represents hydrogen.
- 20
15. A combination as claimed in claim 1, wherein the compound of formula (I) is:-
1,2-dihydro-2-phenyl-4-quinazolinamine;
1,2-dihydro-4-quinazolinamine;
1,2-dihydro-2-methyl-4-quinazolinamine;
25 2-ethyl-1,2-dihydro-4-quinazolinamine;
2-cyclopropyl-1,2-dihydro-4-quinazolinamine;
2-cyclobutyl-1,2-dihydro-4-quinazolinamine;